REMARKS

Amendments:

Drawings

Figures 5, 6, 10a -10b, 11a-11b, 12a, 13a-13d, 14, 15, 16a-16b, 17, 18a-18e, 19a-19b, 21, 22, 23, 24, 25a-25c, 26a-26d, 27a-27d, 28a-28d, 29a - 29b, and 30-36 were amended in Response B, filed May 27, 2003, and explanations for the general nature of the amendments were included in the Remarks section of Response B. In response to the Advisory Action of June 23, 2003, a table has been prepared listing each claim, with its corresponding amendment(s), for clarity, and is attached hereto as Appendix A.

Support for the amendments is as described in Response B, pp. 16-17, and additionally as described below:

Support for the amendments in Figure 13d from "TNF-f to TNF-β," and "MP-9(6) to MMP9"comes from Figures 13a – 13c which depict a gene panel comprised of the same 24 constituents, all of which list TNF-b, not TNF-f, and MMP9 not MP-9(6). Further, as discussed in Response B, amendment of the Arabic b in TNF-b of Figs. 13a-13c to the Greek letter β (and analogous changes in other genes) represents merely a technical change from an informal nomenclature, not a substantive change. Therefore Applicants respectfully submit that the amendments to Fig. 13d do not constitute new matter.

*Support for amendment of "MMP9" to "MMP-9", "pa(2)" to "u-pa(2)", and "TGF-α" to "TNF-α" in Fig. 13d is found in Figs. 13a-13c, which depict the same gene panel comprised of the same 24 genes, including MMP-9, u-pa(2), and TNF- α, and in Substitute Specification, p. 49, line 21, which specifically refers to TNF- α, not TGF- α. Applicants respectfully submit, therefore, that these amendments do not represent new matter.

*Support for amendment of "MMP9" to "MMP-9", and "TGF-α" to "TNF-α" in Fig. 14 is found in Figs. 13a-13c, which depict the same gene panel comprised of the same 24 genes, including MMP-9 and TNF- α, and for the reasons stated above for amendments to Figs. 13d. Applicants respectfully submit, therefore, that these amendments do not represent new matter.

Similarly, support for amendment of "pa-(2)" to "u-pa(2)" and "MP-9(6)" to MMP9 in Fig. 14 is found in Figs. 13a-c, which utilize a gene panel comprised of the same 24 constituents. In addition, p. 65 of the Substitute Specification defines the general gene u-pa as Urokinase-Type Plasminogen Activator and p. 59 defines the general gene mmp9 as Matrix metalloproteinase.

Support for amendment of "IL-11" to "IL-1α" and "IL-10" to "IL-1β" in Fig. 16a is found in Fig. 16b, which utilizes a gene panel comprised of the same 8 constituents. Note that in Fig. 16b, the two genes in the left of the figures are IL-1-a and IL-1-b, not IL-11 and IL-10, as erroneously found in Fig. 16a. Moreover, both Figs. 16a and 16b already have an IL-10 gene (see 5th gene from left) and the IL-11 gene is not disclosed anywhere else in the application (see especially pp. 59-67, Substitute Specification). More importantly, the informal drawings submitted when the application was filed have "IL-1α" and "IL-1β" hand-written over "IL-11" and "IL-10." Applicants respectfully submit that the genes "IL-11" and "IL-10" represent clear error, and as such, amendment to "IL-1α" and "IL-1β" does not represent new matter.

Support for addition of the missing gene label "IL-15" (3rd bar-graph couple from right) in Fig. 16b is found in Fig. 16a at the analogous position. Support for the missing gene label "IL-8" (4th bar-graph couple from the left) in both Figs. 16a and 16b is found in the original informal drawings filed with the application as hand-written labels in both Figs. 16a and 16b. Applicants respectfully submit that as such, these amendments to Figs. 16a and 16b do not constitute new matter.

Support for amendment of "INF-g" to "IFN-γ" in Figs. 18c-18e is found in Figs. 18a-18b (IFN-g). Somehow IFN-g was transposed to INF-g and the change from Arabic "g" to Greek "γ" does not represent a substantive change resulting in addition of new matter.

Support for amendment of "TGF-a" to "TNF-α" in Fig. 19b is found in Figs. 13a-b and 19a, which utilize a panel comprised of the same 24 gene constituents (although those for 19a are listed in a slightly different order). Applicants respectfully submit that this amendment does not constitute new matter.

Support for amendment of "TNF-g" to "IFN-γ," "TPN-b" to TGF-β1," and "Cdx-2" to "Cox-2" in Fig. 22 is found in the genes disclosed in pp. 59-67 of the Substitute Specification wherein only IFN- γ, Cox-2 can be found, not "TNF-g," "TPN-b," and "Cdx-2." In addition, Applicants respectfully submit that the so-called genes "TNF-g," "TPN-b," and "Cdx-2" are clear error and have no meaning to someone of ordinary skill in the art. TNF, which stands for Tumor Necrosis Factor (see Substitute Specification, p. 59, 60, 62, and 65) has not been revealed in the literature to have a gamma form. TPN is not an abbreviation for any known gene, nor is Cdx-2 (which is clearly a typographical error – see Substitute Specification, p. 59 and 65). Therefore, Applicants respectfully submit that these amendments to Fig. 22 do not constitute new matter.

Support for amendment of "SCE" to "SCF" in Fig. 34 is found in original informal Figure 34 submitted when the application was filed, although the F is partially occluded by the black bar graph. Additional support is found in the Substitute Specification on p. 62, wherein the gene SCF is defined as stem cell factor. Applicants respectfully submit that this error was introduced inadvertently by the draftsperson and as such, the amendment does not constitute new matter.

Lastly, support for amendment of "PAI-1 #2" to "PAI-1" is found in the Substitute Specification on p. 65, wherein PAI1 is defined as Plasminogen Activator Inhibitor 1.

For the reasons discussed above, and the reasons set forth in Response B, Applicants respectfully submit that all amendments to the figures do not constitute new matter.

Specification

In Response B, filed May 27, 2003, applicants amended several pages of the specification to correct minor typographical errors and instances of clear error. Although the text for line 27 of Example 16 was amended correctly to add the phrase "five *different* cell lines," the Remarks section of Response B erroneously stated that in line 27 of Example 16 the phrase "five *difference* cell lines" was added (see Response B, p. 18, last full para.). Applicants apologize for any confusion this may have caused and would like to note for the record that Response B should have stated that the phrase "five *different* cell lines" was added.

Applicants respectfully submit that none of the amendments to the specification represent addition, or deletion, of new matter.

Claims

Claim Rejections – 35 USC § 112, para. 1

THE PENDING CLAIMS AS AMENDED CONTAIN NO NEW MATTER

The Examiner has stated in para. 3 of the Advisory Action of June 23, 2003 that claims 167 and 175 contain new matter because no support for a method with the recited limitations in the absence of a calibrated profile data set has been provided, and no support for the limitation in claim 167 of "specificity" being substantially similar for all constituents has been provided. Although Applicants respectfully submit that support for the limitation of "specificity" being substantially similar for all constituents is found in the application on p. 23, line 34 through p.

24, line 4, Applicants have chosen to amend claim 167 to delete the word "specificity" to claim the invention more broadly.

In addition, Applicants submit that the basis for claims 167and 175 in the absence of a calibrated profile data set, and new claims 180-186 are as follows:

Claims 167 and 175. Amended claims 167 and 175 require "deriving ... a profile data set ...; and in deriving ... obtaining such measure ... under conditions that are substantially reproducible ... and efficiencies of amplification for all constituents are substantially similar." Support for these claims is found in the specification on p. 23, lines 6-9 ("We have found that we can measure concentrations ... in a manner that is both highly precise and reproducible ... under the same conditions ... such concentration measurements are reproducible...") and p. 10, lines 14-15 ("... such measurement is performed ... under conditions wherein efficiencies of amplification for all constituents are substantially similar....."

In fact, multiple embodiments of methods requiring only a profile data set, not a calibrated profile data set, are disclosed on p. 10, line 8 through p. 11, line 11 of the application. For example, at p. 10, lines 8 - 15, there is disclosed "a method, for a evaluating a biological condition of a subject, that includes ... deriving from the sample a *profile data set*, the *profile data set* including a plurality of members, each member being a quantitative measure ... in a panel of constituents ... wherein such measurement is performed for each constituent under conditions wherein efficiencies of amplification for all constituents are substantially similar..." (*id.*, lines 8-15, emphasis added). Later, on p. 11, lines 5-7, it is disclosed that "Efficiencies of amplification of all constituents may differ by less than approximately 2%. The efficiencies of amplification of all constituents may differ by less than approximately 1%."

In addition, original claims 156 – 161 are directed to methods that require only a profile

data set, not a calibrated profile data set. For example, claim 156 is directed to "A method, for evaluating a biological condition of a subject, comprising: obtaining from the subject a sample....; deriving from the sample a *profile data set*, the *profile data* set including a plurality of members, each member being a quantitative measure of the amount of a ... constituent in a panel of constituents ... wherein such measure is performed for each constituent under conditions wherein efficiencies of amplification for all constituents are substantially similar, the *profile data set* providing a measure of the biological condition ..." See Application, p. 92, lines 5-14, emphasis added. Further, original claim 157, which depends from claim 156, is directed to "A method according to claim 156, wherein the efficiencies of amplification of all constituents differ by less than approximately 2%." *Id.*, lines 15-16. In light of both the disclosure in the detailed description on pp. 10-11, and original claims 156-161, Applicants respectfully submit that claims 167 and 175 have support in the application and do not constitute new matter.

Response B provided support for new claims 180-184; however, there were actually 7 new claims in Response B, not 5 new claims. Consequently the support listed in Response B was in error. Applicants apologize for the confusion and herein submit that support for new claims 180 – 186, which depend variously from claims 167 and 175, can be found in the specification as follows:

Claims 180-181 and claims 183-184: p. 10, line 8 through p. 11, line 4; and p. 23, lines 6-20.

Claim 182 and claim 185: p. 22, line 37 through p. 23, line 2.

Claim 186: p. 26, lines 13-16.

In light of the above arguments, Applicants respectfully submit that there is support in the specification for all the limitations in claims 165and 175 and new claims 180-186 and therefore no new matter has been added.

In summary, the claims, as amended, have support in the specification and do not contain new matter. Further, for the reasons stated in Response B, the claims are enabled for someone of ordinary skill in the art and the specification, as written, does not require undue experimentation to practice the invention.

The cited reference, Rodriguez-Antona et al., does not contain every element of the claims and so does not anticipate the presently claimed invention. Moreover, the cited reference does not teach these elements either, and so does not render the present claims obvious.

CONCLUSION

For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Applicants do not believe that an extension of time is required; however, this conditional petition for an extension of time is being made in the event that the need for an extension has been overlooked. Please pay any fees required for the timely consideration of this application from deposit account number 19-4972. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

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Respectfully submitted,

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APPENDIX A

Figure #	AMENDMENTS MADE		
Figure 5	Figure title: "Precision" to "Selected"		
Figure 6	Figure boxes: "Precision" to "Selected"		
Figure 10a	Figure title: "Precision" to "Selected"		
Figure 10b	Figure title: "Precision" to "Selected"		
Figure 11a		IL-1 ALPHA, IL-1 BETA, IFN gamma, INF alpha to IL-1α, IL-1β, IFN-γ, and IFN-α	
Figure 11b		IL-1 ALPHA, IL-1 BETA, IFN gamma, INF alpha to IL-1α, IL-1β, IFN-γ, and IFN-α	
Figure 12a		IL-1a, IFN-GAMMA, TNF-a to IL-1α, IFN-γ, and TNF-α	
Figure 13a		IL-1-a, IL-1-b, IFN-g, TGF-b, TNF-a, TNF-b to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α, TNF-β	
Figure 13b		IL-1-a, IL-1-b, IFN-g, TGF-b, TNF-a, TNF-b to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α, TNF-β	
Figure 13c		IL-1-a, IL-1-b, IFN-g, TGF-b, TNF-a, TNF-b to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α, TNF-β	
Figure 13d		IL-1-a, IL-1-b, IFN-g, TGF-b, TGF-a, TNF-f to IL-1α, IL-1β, IFN-γ, TGF-β, TGF-α, TNF-β	
Figure 14		IL-1-a, IL-1-b, IFN-g, TGF-b, TGF-a, TNF-b, MP-9(6), pa(2) to IL-1α, IL-1β, IFN-γ, TGF-β, TGF-α, TNF-β, MMP9, u-pa(2)	
Figure 15		IL-1-a, IL-1-b, IFN-g, TNF-a to IL-1α, IL-1β, IFN-γ, TNF-α	
Figure 16a		IL-11, IL-10, IFN-gamma, TNF-a to IL-1α, IL-1β, IFN-γ, TNF-α;	Insert missing IL-8 label for bar-graph pair 4th from left

Figure #	AMENDMENTS MADE		
Figure 16b		IL-1-a, IL-1-b, IFN-ga, TNF-a to IL-1α, IL-1β, IFN-γ, TNF-α	Insert missing IL-8 label for bar-graph pair 4th from left and missing gene label "IL-15" for 3rd bar-graph pair from right
Figure 17		IL-1-a, IL-1-b, IFN-g, TGF-b, TNF-a, TNF-b to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α, TNF-β	
Figure 18a		IL-1-a, IFN-g to IL-1-α, IFN-γ	ug/mL to μg/mL and uM to μM in Figure Legend Inset
Figure 18b		IL-1-a, IFN-g to IL-1-α, IFN-γ	ug/mL to μg/mL and uM to μM in Figure Legend Inset
Figure 18c		IL-1-a, INF-g to IL-1-α, IFN-γ	ug/mL to μg/mL and uM to μM in Figure Legend Inset
Figure 18d		IL-1-a, INF-g to IL-1-α, IFN-γ	uM to μM in Figure Legend Inset
Figure 18e		IL-1-a, INF-g to IL-1-α, IFN-γ	ug/mL to μg/mL and uM to μM in Figure Legend Inset
Figure 19a		IL-1ALPHA, IL-1BETA, IFN-GAMMA, TGF-BETA, TNF-alpha, TNF-beta to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α, TNF-β	
Figure 19b		IL-1-a, IL-1-b, IFN-g, TGF-b, TGF-a, TNF-b to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α, TNF-β	
Figure 21		IFNa, IL-1-B to IFN-α, IL- β	ug/ml to μg/mL in Figure Legend Inset
Figure 22		IL-1a, IL-1b, TNF-g, TPN-b, TNF-a, TNF-b, Cdx-2 to IL-1α, IL-1β, TNF-γ, TGF-β, TNF-α, TNF-β, Cox-2	
Figure 23	Figure title: "Precision" to "Selected"	TNF-a, IL-1-B, IFNg to TNF-α, IL-1β, IFN-γ	ug/ml to μg/mL in Figure Legend Inset
Figure 24	Figure title: "Precision" to "Selected"	IL-1a, IL-1B, TNF-a to IL-1α, IL-1β, TNF-α	
Figure 25a		IL-1 alpha, IL-1 beta, IFN-gamma, TGF-beta, TNF-alpha to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α	ug/ml to μg/mL in Figure Legend Inset
Figure 25b		IL-1 alpha, IL-1 beta, IFN-gamma, TGF-beta, TNF-alpha to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α	ug/ml to μg/mL in Figure Legend Inset

Figure #	AMENDMENTS MADE		
Figure 25c	Figure title: "Precision" to "Selected"	IL-1 alpha, IL-1 beta, IFN-gamma, TGF-beta, TNF-alpha to IL-1α, IL-1β, IFN-γ, TGF-β, TNF-α	
Figure 26a	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 26b	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 26c	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 26d	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 27a	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 27b	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 27c	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 27d	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, IFN-g to TNF-α, IL-1α, IL-1β, IFN-γ	
Figure 28a	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, to TNF-α, IL-1α, IL-1β,	
Figure 28b	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, to TNF-α, IL-1α, IL-1β,	
Figure 28c	Figure title: "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, to TNF-α, IL-1α, IL-1β,	
Figure 28d	Figure title : "Precision" to "Selected"	TNF-a, IL-1-a, IL-1-b, to TNF-α, IL-1α, IL-1β,	
Figure 29a	Figure title : "Precision" to "Selected"	IL-1a, IL-1b, IFN-9, TNF-a to IL-1α, IL-1β, IFN-γ, TNF-α	Lower labels for each bar-graph couple are rotated 180° counter-clockwise
Figure 29b	Figure title : "Precision" to "Selected"	IL-1a, IL-1b, IFN-9, TNF-a to IL-1α, IL-1β, IFN-γ, TNF-α	Lower labels for each bar-graph couple are rotated 180° counter-clockwise
Figure 30	Figure title : "Precision" to "Selected"	TNF-a, TGF-beta to TNF-α, TGF-β	Internal labels for each bar-graph couple are rotated 180° counter-clockwise
Figure 31	Figure title: "Precision" to "Selected"	Lower label (6 MALE RATS, 100 mg/kg/day, po 4days) to (6 MALE RATS, 400 mg/kg/day, po 4days)	

Figure #	AMENDMENTS MADE		
Figure 32	Figure title: "Precision" to "Selected"		
Figure 33	Figure title: "Precision" to "Selected"	IL-1alpha, IL-1beta, Nfkbeta, TNFalpha, TGFbeta to IL-1α, IL-1β, NF-κβ, TNF-α, TGF-β	TNFalpha 10ng/ml to TNF-α 10 ng/mL in Figure Legend Inset
Figure 34	Figure title: "Precision" to "Selected"	PPARa, SCF to PPAR-α, SCE	uM to μM in Figure Legend Inset
Figure 35	Figure title: "Precision" to "Selected" and TNF-a to TNF-α	IL-1b, PAI-1 #2, NFkB, to IL-1β, PAI-1, NF-κβ	ng/ml to ng/mL in Figure Legend Inset
Figure 36	Figure title: "Precision" to "Selected"	IL-1A, IL-1B, TNF-A, TGF-B to IL-1α, IL-1β, TNF-α, TGF-β	
*Figure 13d (amended herein)		pa(2), MMP9, and TGF-α to u-pa(2), MMP-9, and TNF-α	
*Figure 14 (amended herein)		MMP9 and TGF-α to MMP-9, and TNF-α	